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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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3/30/00

In re Application of:
Mar Tormo
Ana M. Tari
Gabriel Lopez-Berestein

Serial No.: 08/726,211

Filed: October 4, 1996

For: INHIBITION OF BCL-2 PROTEIN EXPRESSION BY LIPOSOMAL ANTISENSE OLIGODEOXYNUCLEOTIDES

Group Art Unit: 1636

Examiner: R. Schwartzman

Atty. Dkt. No.: UTXC:504/STA

CERTIFICATE OF MAILING
37 C.F.R. §1.8

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March 21, 2000
Date

Jonathan D. Hurt

BRIEF ON APPEAL

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APPEAL BRIEF

BOX AF
Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Appellants hereby submit an original and two copies of this Appeal Brief to the Board of Patent Appeals and Interferences in response to the final Office Action ("the Action") dated July 16, 1999. A Notice of Appeal was mailed December 16, 1999. The Office date of receipt of the Notice of Appeal, which begins the period from which the due date for this Brief (M.P.E.P. § 1206), was December 21, 1999. The two-month date for filing this Appeal Brief was February 21, 2000.

A request for a one-month extension of time to respond is included herewith along with the required fee. This one-month extension will bring the due date to March 21, 2000.

The fee for filing this Appeal Brief and the fee for the extension of time is attached hereto. If the check is inadvertently omitted, or should any additional fees under 37 C.F.R.

§§ 1.16 to 1.21 be required for any reason relating to the enclosed material, or should an overpayment be included herein, the Assistant Commissioner is authorized to deduct or credit said fees from or to Fulbright & Jaworski L.L.P. Deposit Account No. 50-1212/UTXC:504/STA.

I. REAL PARTY IN INTEREST

The real party in interest in this appeal is the Assignee of the application Board of Regents, The University of Texas System, 201 West 7th Street, Austin, Texas 78701.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences pending in regard to this technology.

III. STATUS OF THE CLAIMS

This application was filed October 4, 1996. Claims 1-20 were originally filed in this application. In an amendment filed December 8, 1997, claims 1-3, 6, 9-10, 13, and 15-16 were amended. In an amendment filed June 12, 1998, claims 1 and 9-10 were amended, and claims 21-37 were added. In another amendment filed November 11, 1998, claims 1 and 21 were amended and claims 38-55 were added. In an amendment filed June 4, 1999, claims 1, 9, 31 and 52 were amended. Claims 42 and 51 were cancelled without prejudice or disclaimer, and claim 56 was added. In the final Official Action dated July 16, 1999 ("the Action"), claims 1-41, 43-50 and 52-56 were rejected. Appellants submitted an amendment filed September 16, 1999, wherein claims 1, 9, 31 and 52 were amended.

In the Advisory Action dated October 5, 1999, the amendments to claims 1, 9, 31 and 52 were stated as being entered upon filing of a Notice of Appeal and Appeal Brief. A Notice of

Appeal was filed December 16, 1999. The Advisory Action withdrew the rejections of claims 38, 43, 45, 47 and 55, though these claims are objected to. Claims 1-37, 39-41, 44, 46, 48-50, 52-54 and 56 are currently rejected.

Appendix A contains the claims under appeal, in what Appellant believes to be the correct status after entry of the amendment submitted in conjunction with this brief. Claims 1-41, 43-50 and 52-56 are pending.

IV. STATUS OF AMENDMENTS

An amendment was filed September 16, 1999, in response to the final Office Action. In the Advisory Action dated October 5, 1999, the amendments to claims 1, 9, 31 and 52 were stated as being entered upon filing of a Notice of Appeal and Appeal Brief. A Notice of Appeal was filed December 16, 1999. Therefore, these amendments should be entered upon receipt of this paper.

V. SUMMARY OF THE INVENTION

This invention generally involves Appellant's discovery that an antisense polynucleotide complementary to the translation initiation site of Bcl-2 can be combined with a neutral lipid to form a neutral lipid/polynucleotide association that will hybridize to a Bcl-2-encoding polynucleotide under intracellular conditions. Specification at page 4, lines 11-27. The invention is surprising and unexpected in that neutral lipid/Bcl-2 associations do not possess cellular toxicity of charged lipid/Bcl-2 associations and thereby exhibit superior properties. Specification at page 7, lines 12-22, specification at page 37, lines 3-8, FIG. 1 and FIG. 2.

VI. ISSUES ON APPEAL

The issues for the Board's consideration are:

(a) whether claims 1-9, 31-37, 39-41, 48-50 and 52-54 are properly rejected under 35 U.S.C. §103(a) as obvious over Evan or Reed or Green *et al.* in view of Tari *et al.*; and

(b) whether claims 1-8, 10-36, 39, 44, 48-50, 52-54 and 56 are properly rejected under 35 U.S.C. §103(a) as obvious over Abubakr *et al.*, Pocock *et al.* and Cotter *et al.* in view of Tari *et al.* and in further view of Evan

VII. GROUPING OF THE CLAIMS

For the purposes of this appeal, the claims stand or fall together.

VIII. SUMMARY OF ARGUMENT

The examiner continues to maintain the rejection of claims 1-37, 39-41, 44, 46, 48-50, 52-54 and 56 over a variety of references in view of Tari *et al.* Throughout this prosecution, it has been Appellants' position that Tari *et al.* does not teach or suggest that neutral lipids possess the surprising and unexpected property of non-toxicity to relative to lipids-in-general or charged lipids. Appellants have provided out in the specification and via declaration's data that supports the finding of this novel and non-obvious property. The cited references, either alone or in combination, fail to direct one of skill in the art to the claimed invention, as they do not teach or suggest this property.

IX. ARGUMENT

A. Rejection of Claims 1-9, 31-37, 39-41, 48-50, 52-54 and 56 Under 35 U.S.C. § 103(a) over Evan or Reed or Green *et al.* in View of Tari *et al.*

Claims 1-9, 31-37, 39-41, 48-50, 52-54 and new claim 56 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious in light of Evan (WO 93/20200) or Reed (WO 95/08350) or Green *et al.* (U.S. Patent No. 5,583,034) in view of Tari *et al.* (U.S. Patent No. 5,417,978). Appellants respectfully traverse. The claimed invention is not obvious relative to these references, either alone or in combination.

This rejection was first made regarding claims 1-9 in the office action dated March 16, 1998. There, the examiner argued that the Evan or Reed or Green *et al.* references teach antisense oligonucleotides targeted to Bcl-2, but do not teach a liposome made of neutral lipids. The examiner argued that Tari *et al.* teaches an antisense oligonucleotide encapsulated in a liposome, and liposomes comprising phosphatidylcholine or phosphatidylserine, with dioleoylphoshpatidycholine preferred. Thus, the examiner proposed that it would have been obvious to combine an antisense Bcl-2 oligonucleotide of Evan, Reed or Green *et al.* with Tari *et al.*'s liposomes comprising dioleoylphosphatidycholine, with an eye towards improving stability and cellular uptake. This rejection has been subsequently maintained through the Action dated July 16, 1999 and the Advisory Action dated October 5, 1999, and currently encompasses claims 1-9, 31-37, 39-41, 48-50, 52-54 and 56.

The presently claimed invention is directed to uncharged liposome compositions comprising Bcl-2 related antisense constructs, and methods of use therefor. Regarding the teachings of Tari *et al.*, Appellants disagree with the examiner's conclusions. At best, this

references teaches the benefits of liposomal compositions ***in general***. Tari *et al.* does not provide critical teachings or suggestions that would lead the skilled artisan to adopt neutral, as opposed to charged, liposomes. Thus, the examiner is improperly interpreting the reference. Further, appellants have demonstrated that charged liposomes, as a class, are toxic, and that uncharged liposomes are non-toxic. Again, appellants find no such teaching in Tari *et al.*, as alleged by the examiner. As such, appellants respectfully submit that the rejection is based on an improper reading and application of Tari *et al.*

Tari et al. Teaches That All Liposomal Formulations Are Useful

Tari *et al.* clearly teaches the use of liposomal compositions ***broadly***, as described at column 1, line 65 to column 2, line 3:

> The present invention relates to a liposomal methyl phosphonate oligonucleotide composition. The composition comprises (a) a liposome which comprises at least one phospholipid, and (b) an antisense methyl phosphonate oligonucleotide which is entrapped in the liposome.

Tari *et al.* additionally describes liposomes as including various "suitable" phospholipids, at column 3, lines 41-48:

> "Liposomes" is used in this patent to mean lipid-containing vesicles having a lipid bilayer, as well as other lipid carrier particles which can entrap antisense oligonucleotides. The liposomes can be made of one or more phospholipids, optionally including other materials such as sterols. Suitable phospholipids include phosphatidyl cholines, phosphatidyl serines, and many others that are well known in this field.

Tari *et al.* teaches that liposome constructs in general are useful and possess desirable properties, at column 2, lines 49-56:

> The advantages of the invention include improved stability of the antisense oligonucleotides compositions under biologic conditions, improved uptake of the composition in cells, improved incorporation efficiency of the oligonucleotides into liposomes, and enhanced specific therapeutic effect of the antisense

> oligonucleotides against CML and other disease conditions in which similar gene rearrangements are observed.

Appellants respectfully submit that these teachings point to liposomal compositions generally, and do not identify particular lipids, by class, for use in conjunction with the delivery of oligonucleotides, or any other composition for that matter.

Tari et al. Does Not Point To Neutral Lipids As Being Non-Toxic As A Class

Phoshatidyl cholines are uncharged lipids, and phosphatidyl serines are charged lipids. Tari *et al.* describes phosphatidyl serines, as preferred lipids, and phosphatidyl cholines as preferred or particularly preferred, at column 2, lines 10-14.

> In preferred embodiments of the invention, the at least one phospholipid is selected from the group consisting of phosphatidyl cholines and the phosphatidyl serines, with dioleoyl phosphatidyl choline being a particularly preferred lipid.

One experiment, shown at Table 4, demonstrated that dioleoyl (C18:1) phosphatidylserine, a charged lipid, incorporates MP as well, within statistical error, as the best phospatidylcholine composition tested. The majority of examples described in Tari *et. al.* focused on phosphatidyl choline (PC). As described at column 5, lines 18-22, phoshatidyl choline was selected for use in the majority of experiments incorporating methyl phosphonate oligonucleotides (MP) because:

> (1) both PC and MP are neutral molecules, so they should be compatible and (2) PC is well-studied lipid and easy to handle.

Empty liposomes containing phoshatidyl choline were described as not inhibiting growth in BV173 cells, at column 7, lines 14-16 and 34-36 and at column 7, line 58 to column 8, line 2.

However, Appellants do not find that Tari *et al.* teaches or suggests that the lack of inhibition of growth by phoshatidyl choline was a trait *specific* to phosphatidyl choline, much less to neutral lipids. As described above, Tari *et al.* teaches liposomes in general, and the

choice of phosphatidyl choline for the experiments described were based on properties ***other than toxicity***. Appellants find no mention or suggestion in Tari *et al.* that the toxicity of neutral lipids is generally less than other classes such as charged lipids. However, this is the very premise upon which the rejection is based. Its refutation here is strong evidence that the rejection is improper.

The Superior Non-Toxicity Properties of the Claimed Invention over the Compositions of Tari et al. Has Been Demonstrated

In an earlier response, appellants provided a declaration from inventors Tari and Lopez-Berestein (attached as Exhibit A). This declaration presents data clearly demonstrating the non-specific toxicity of charged liposomes to the tested cell lines, and the lack of toxicity for uncharged liposomes. This data is surprising and unexpected because it demonstrates the advantage of the presently claimed invention over the teachings of Tari *et al.* of liposomal compositions in general. Such evidence refutes the case for obviousness:

> Office personnel should not require the applicant to show unexpected results over the entire range of properties possessed by a chemical compound or composition. See *e.g.*, *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987). Evidence that the compound or composition possesses superior and unexpected properties in one of a spectrum of common properties can be sufficient to rebut a *prima facie* case of obviousness.

M.P.E.P. 2144.08(II)(B).

The declaration of. Tari and Lopez-Berestein demonstrates the surprising and unexpected properties of the claimed invention over the compositions of the prior art. In the table at page 3, the desired selective cytotoxicity of the neutral liposomes-BCL-2 antisense oligonucleotide composition, the relative non-toxicity of neutral (*i.e.*, DOPC) liposomes containing a control Bcl-2 oligonucleotide, and the non-specific cytotoxicity of liposomes containing 30% negatively

charged lipids (DOPC-DMPG) or 30% positively charged lipids (DOPC-DC-CHOL) with either Bcl-2 antisense or control oligonucleotides, are illustrated.

This declaration supports the teachings of the specification with regard to selective toxicity to target cells and non-toxicity to other cell types. For example, as demonstrated in the specification at page 7, lines 12-16 and FIG. 1, liposomes comprising neutral lipids and a Bcl-2 oligonucleotide are selectively toxic to cells containing a t(14;18) translocation. This property is further demonstrated in the results showing that liposomes comprising neutral lipids, with or without a non-Bcl-2 oligonucleotide, are relatively non-toxic to either target or control cell lines, at page 7, lines 17-22 and in Fig. 2. The evidence of the non-toxicity of liposomes comprising neutral lipids is further described at page 37, lines 3-8:

> Two control oligonucleotides were used to determine the specificity of the inhibition observed. When L-control oligos or empty liposomes were added to Johnson cells, cell growth inhibition was not observed. Jurkat, Raji and Daudi cells were also treated with L-control oligos and empty liposomes. Non-specific toxicity could be observed when greater than 6 μmol/L of L-OS were used, ***but not with empty liposomes*** (FIG. 2). (Emphasis added).

There is nothing in any of the cited references that would have led the skilled artisan to believe that these results would have flowed *a priori* from the use of liposomes constructed from neutral lipids and Bcl-2 antisense constructs.

The Action's Arguments Relies upon Hindsight Reconstruction

The Action argues that the "showing in the declaration ... cannot be considered surprising ... as Tari *et al.* showed that DOPC-based liposomes were effective and non-toxic." However, appellants' invention is not limited to DOPC, but is drawn to neutral lipids generally. Thus, appellants submit that the ***claimed invention*** is surprising. To argue otherwise relies upon the impermissible use of hindsight. *In re Carroll*, 202 U.S.P.Q. 571 (CCPA 1979) ("One of the

more difficult aspects of resolving questions of non-obviousness is the necessity 'to guard against slipping into the use of hindsight.'"), citing *Graham v. John Deere Co.*, 148 U.S.P.Q. 459 (U.S. S. Ct. 1965). Appellants submit that it is incumbent upon the examiner to find the teaching or suggestion in the primary reference that ***uncharged liposomes are non-toxic relative to charged liposomes or liposomes in general***, something which the examiner has failed to do here. *In re Soli*, 137 U.S.P.Q. 797, 801 (CCPA 1963).

The Action Failed to Compare the Declaratory Evidence with the Teachings of Tari et al.

The Action argues at page 9 that "no comparison can be made between the results shown in the declaration and the teachings of Tari *et al.*" because "liposomes comprising 30% positively- or negatively-charged lipids cannot be said to be surprising in view of Tari *et al.* as Tari *et al.* never tested the liposomes containing DOPS .... Tari *et al* never tested the liposomes containing DOPS for their effect on cells." However, by acknowledging that Tari *et al.* failed to explore the toxicity of DOPS liposomes, the examiner admits that the prior art is deficient in establishing the generalized detriment of charged liposomes, and hence the generalized benefit of charged liposomes. This actually argues ***against*** obviousness of the presently claimed compositions and methods.

The Action also argues at page 9 that the declaratory evidence "would only demonstrate an unexpected disadvantage of what is not being presently claimed, not an unexpected advantage of what is presently claimed." However, where the prior art suggest use of a genus, and the present invention claims a species with a desireable, yet unheralded property, the invention cannot be said to be obvious over the art.

The Declaratory Evidence Has Not Been Given Proper Consideration

The examiner also has failed to properly consider the previously submitted declaration of Tari and Lopez-Berestein in its evaluation of obviousness or non-obviousness of the claimed invention in light of the cited art. The examiner "should consider all rebuttal arguments and evidence presented by applicants." *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995); MPEP §2144.08 B. Appellants declaration demonstrates the surprising and unexpected properties of the claimed invention over the teachings of the cited references, and should be given substantive weight.

Appellants contend that all relevant prior art teachings must be considered in evaluation of obviousness. See MPEP §2144.08(II)(A)(4). Tari *et al.* teaches, at column 2, lines 53-55, "an enhanced **specific** therapeutic effect of the antisense oligonucleotides" of its invention, which includes both charged and uncharged liposomal constructs. (Emphasis added). The data presented in this declaration demonstrates that charged liposomes are non-specifically toxic to the tested cell lines. This data is surprising and unexpected because it demonstrates the advantage of the presently claimed invention over the teachings of Tari *et al.* ***as a whole.***

> One way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of "unexpected results," *i.e.*, to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected [because] that which would have been surprising would not have been obvious. The principle applies most often to predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results.

In re Soni, 54 F.3d 746, 750 (Fed. Cir. 1995). Appellants contend that, in light of the full teachings of the benefits of both neutral and charged liposomes by Tari *et al.*, the evidence of surprising and unexpected advantages associated with the use of antisense Bcl-2 oligonucleotides associated specifically with neutral lipids rebuts any asserted *prima facie* case of obviousness.

The References Posit Insufficient Motivation to Select Neutral Lipids

The Action also fails in supporting the argument that Tari *et al.* provides the proper motivation to combine its teachings with Evan, Reed and Green to specifically select neutral lipids for combination with the oligonucleotides of the claimed invention. The Action argues at page 5 that the motivation to combine the "liposomal formulation taught by Tari *et al.*" was the teaching of Tari *et al.* that 'liposomes comprising dioleoylphosphatidylcholine impart improved stability and cellular uptake to the antisense oligonucleotides." This is a mischaracterization of the teachings of Tari *et al.* Tari *et al.* teaches a "liposomal methyl phosphonate oligonucleotide composition," as described at column 1, line 65 to column 2, line 3:

> The present invention relates to a liposomal methyl phosphonate oligonucleotide composition. The composition comprises (a) a liposome which comprises at least one phospholipid, and (b) an antisense methyl phosphonate oligonucleotide which is entrapped in the liposome.

The Action attributes the properties of "improved stability and cellular uptake" to dioleoylphosphatidylcholine, when Tari *et al.* teaches that these properties are common to all liposome constructs disclosed in Tari *et al.*, at column 2, lines 49-56:

> The advantages of the invention include improved stability of the antisense oligonucleotides compositions under biologic conditions, improved uptake of the composition in cells, improved incorporation efficiency of the oligonucleotides into liposomes, and enhanced specific therapeutic effect of the antisense oligonucleotides against CML and other disease conditions in which similar gene rearrangements are observed.

Again, it is submitted that the advantages referred to by the Action ***are disclosed in regards to all liposome constructs described by Tari et al.***, without a teaching, suggestion or guidance to use either charged or neutral lipids, let alone specifying the lipid dioleolphosphatidylcholine. Thus, this teaching does not provide the necessary guidance to a neutral lipid to combine this reference with the other cited references.

Appellants respectfully request that this rejection be withdrawn.

B. The Rejection of Claims 1-8, 10-36, 39, 44, 46, 48-50, 52-54 and 56 Under 35 U.S.C. § 103(a) Over Abukarkr *et al.*, Pocock *et al.* and Cotter *et al.* in view of Tari *et al.* Is Overcome

Claims 1-8, 10-36, 39, 44, 46, 48-50, 52-54, and new claim 56, are rejected under 35 U.S.C. §103(a) over Abubakr *et al.* (*Blood* 82 (10 Suppl. 1) 374a, Abstract #1481), Pocock *et al.* (*Blood* 82 (10 Suppl. 1, 200A, Abstract #784) and Cotter *et al.* (*Oncogene*, 9:3049-3055, 1994) as allegedly being obvious in view of Tari *et al.* (U.S. Patent No. 5,417,978). Appellants respectfully traverse. The claimed invention is not obvious relative to these references, either alone or in combination.

As with the rejection of the claims described above in section VIII(A) of this paper, Appellants respectfully submit that the Office, in its arguments for obviousness, has failed to evaluate Tari *et al.* as a whole relative to the teachings of the specification and the declaratory evidence previously presented.

In regards to the additionally cited references, the Action has admitted that Abubakr *et al.*, Pocock *et al.*, and Cotter *et al.*, do not teach "administration of the antisense oligonucleotide as a composition comprising neutral lipids." The Action again relies on the teachings of Tari *et al.* to provide the motivation for combining the teachings of all these references. The Action states at page 11 that one of ordinary skill in the art would be "motivated by the teaching of Tari *et al.* that the neutral lipid composition impart several benefits." This is incorrect, as Tari *et al.* teaches that these properties are common to all liposome constructs, at column 2, lines 49-56. As described in section IX(A) of this paper, the teachings in Tari *et al.* of lipids in general, when evaluated as a whole, does not provide the necessary guidance to a neutral lipid to combine this reference with the other cited references.

Even if Tari *et al.* was combined with these references, Appellants submit that the Action's obviousness rejection similarly fails in light of the declaratory evidence and teaching of the specification. Further, given the superior properties demonstrated in cell culture of neutral lipid/Bcl-2 antisense oligonucleotide compositions over the teaching of the cited references, the claimed methods of use for neutral lipid compositions in claims 10-30 is non-obvious relative to Tari *et al.* either alone or in combination with Abubakr *et al.*, Pocock *et al.*, and Cotter *et al.*

The teachings of the specification and the evidence provided by Appellants compels a finding of non-obviousness over Tari *et al.*, either alone or in combination with Abubakr *et al.*, Pocock *et al.*, and Cotter *et al.*

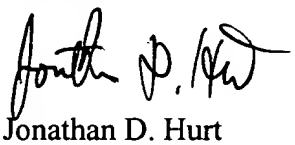
Appellants respectfully request that this rejection be withdrawn.

X. CONCLUSION

Appellant has submitted arguments which overcome the pending rejections. Appellant respectfully submits that the Action's conclusions that the claims should be rejected are unwarranted. It is therefore requested that the Board overturn the Action's rejections.

Please date stamp and return the enclosed postcard to evidence receipt of this document.

Respectfully submitted,



Jonathan D. Hurt
Reg. No. 44,790
Agent for Appellants

FULBRIGHT & JAWORSKI L.L.P
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 418-3000

Date: March 21, 2000

APPENDIX 1 – CLAIMS ON APPEAL

1. A composition comprising a first antisense polynucleotide that hybridizes to a second, Bcl-2-encoding polynucleotide under intracellular conditions and a neutral lipid associated with said first polynucleotide, to form a Bcl-2 polynucleotide/neutral lipid association, wherein said first polynucleotide comprises at least 8 nucleotides of the sequence CAGCGTGCGCCATCCTTC (SEQ ID NO:1), wherein said polynucleotide is complementary to the translation initiation site of Bcl-2.

2. The composition of claim 1, wherein said first polynucleotide is an oligonucleotide having a length of between about 8 and about 50 bases.

3. The composition of claim 1, wherein the first polynucleotide is complementary to the translation initiation site of Bcl-2 mRNA.

4. The composition of claim 3, wherein the polynucleotide is an oligonucleotide comprising the sequence CAGCGTGCGCCATCCTTC (SEQ ID NO:1).

5. The composition of claim 1, comprising a liposome formed from the lipid.

6. The composition of claim 5, wherein the first polynucleotide is encapsulated in the liposome.

7. The composition of claim 1, wherein the lipid is a phosphatidylcholine, a phosphatidylglycerol, or a phosphatidylethanolamine.

8. The composition of claim 7, wherein the lipid is dioleoylphosphatidylcholine.

9. A composition comprising an expression construct that encodes a first antisense polynucleotide that hybridizes to a second, Bcl-2-encoding polynucleotide under intracellular conditions, wherein said construct is under the control of a promoter that is active in eukaryotic cells and associated with a neutral lipid, wherein said first polynucleotide comprises at least 8 nucleotides of the sequence CAGCGTGCGCCATCCTTC (SEQ ID NO:1), wherein said polynucleotide is complementary to the translation initiation site of Bcl-2.

10. A method of inhibiting proliferation of a Bcl-2-associated disease cell comprising obtaining a first polynucleotide that hybridizes to a second polynucleotide under intracellular conditions, mixing the first polynucleotide with a neutral lipid to form a composition comprising a polynucleotide/lipid association, and administering said association to said Bcl-2-associated disease cell to inhibit the proliferation of said disease cell, wherein said cell has a t(14;18) translocation, and wherein the second polynucleotide comprises at least 8 bases of the translation initiation site of Bcl-2 mRNA.

11. The method of claim 10, wherein the cell is a cancer cell.

12. The method of claim 11, wherein said cancer cell is a follicular lymphoma cell.

13. The method of claim 10, wherein said first polynucleotide is an oligonucleotide having a length of between about 8 and about 50 bases.

14. The method of claim 10, comprising a liposome formed from the lipid.

15. The method of claim 14, wherein the liposome encapsulates the first polynucleotide.

16. The method of claim 10, wherein said administering takes place in an animal.

17. The method of claim 16, wherein said animal is a human.

18. The method of claim 17, wherein said composition is delivered to said human in a volume of 0.50-10.0 ml per dose.

19. The method of claim 17, wherein said composition is delivered to said human in an amount of from about 5 to about 30 mg polynucleotide per m^2.

20. The method of claim 19, wherein said composition is administered three times per week for eight weeks.

21. A method of inhibiting proliferation of a Bcl-2-associated disease cell having a t(14;18) translocation comprising:

(a) obtaining an oligonucleotide of from about 8 to about 50 bases and complementary to at least 8 consecutive bases of the translation initiation site of Bcl-2 mRNA;

(b) mixing the oligonucleotide with a neutral lipid to form a neutral oligonucleotide/lipid association; and

(c) administering said association to said Bcl-2-associated disease cell to inhibit the proliferation of said disease cell.

22. The method of claim 21, wherein the cell is a cancer cell.

23. The method of claim 22, wherein said cancer cell is a follicular lymphoma cell.

24. The method of claim 21, comprising a liposome formed from the lipid.

25. The method of claim 24, wherein the liposome encapsulates the polynucleotide.

26. The method of claim 21, wherein said administering takes place in an animal.

27. The method of claim 26, wherein said animal is a human.

28. The method of claim 27, wherein said composition is delivered to said human in a volume of 0.50-10.0 ml per dose.

29. The method of claim 27, wherein said composition is delivered to said human in an amount of from about 5 to about 30 mg polynucleotide per m^2.

30. The method of claim 29, wherein said composition is administered three times per week for eight weeks.

31. A neutral lipid oligonucleotide association comprising a neutral lipid associated with an antisense oligonucleotide of from about 8 to about 50 bases and complementary to the translation initiation site of Bcl-2 mRNA, wherein said translation initiation site comprises the sequence CAGCGTGCGCCATCCTTC (SEQ ID NO:1).

32. The neutral lipid oligonucleotide association of claim 31, wherein the oligonucleotide has the sequence CAGCGTGCGCCATCCTTC (SEQ ID NO:1).

33. The neutral lipid oligonucleotide association of claim 31, comprising a liposome formed from the lipid.

34. The neutral lipid oligonucleotide association of claim 33, wherein the oligonucleotide is encapsulated in the liposome.

35. The neutral lipid oligonucleotide association of claim 31, wherein the lipid is a phosphatidylcholine, a phosphatidylglycerol, or a phosphatidylethanolamine.

36. The neutral lipid oligonucleotide association of claim 35, wherein the lipid is dioleoylphosphatidylcholine.

37. A composition comprising a neutral lipid associated with an expression construct that encodes an oligonucleotide of from about 8 to about 50 bases and complementary to at

least 8 bases of the translation initiation site of Bcl-2 mRNA, wherein the construct is under the control of a promoter that is active in eukaryotic cells.

39. The composition of claim 5, wherein said liposome consists essentially of neutral lipids.

40. The composition of claim 9, comprising a liposome formed from said neutral lipid.

41. The composition association of claim 40, wherein said liposome consists essentially of neutral lipids.

44. The method of claim 14, wherein said liposome consists essentially of neutral lipids.

46. The method of claim 24, wherein said liposome consists essentially of neutral lipids.

48. The neutral lipid oligonucleotide association of claim 33, wherein said liposome consists essentially of neutral lipids.

49. The composition of claim 37, comprising a liposome formed from the lipid.

50. The composition of claim 49, wherein said liposome consists essentially of neutral lipids.

52. A composition comprising a first antisense polynucleotide that hybridizes to a second, Bcl-2-encoding polynucleotide under intracellular conditions and a primary phosphatide associated with said first polynucleotide, wherein said primary phosphatide is a neutral lipid, and wherein said first polynucleotide comprises at least 8 nucleotides of the sequence CAGCGTGCGCCATCCTTC (SEQ ID NO:1), and wherein said polynucleotide is complementary to the translation initiation site of Bcl-2.

53. The composition of claim 52, comprising a liposome formed from the primary phosphatide.

54. The composition of claim 53, wherein said liposome consists essentially of neutral lipids.

56. The composition of claim 1, wherein said at least 8 nucleotides are consecutive nucleotides.

APPENDIX 2 - TABLE OF AUTHORITIES

APPENDIX 3 - EXHIBITS